2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO STRONTIUM IN THE UNITED STATES

Stable Strontium.

Strontium, a nonessential trace element (atomic number 38), is one of the alkaline earth metals with chemical similarities to calcium. Strontium occurs naturally as a mixture of four stable isotopes, ^{88}Sr, ^{86}Sr, ^{87}Sr, and ^{84}Sr, with an abundance by weight of 82.58, 9.86, 7.00, and 0.56%, respectively. Strontium comprises approximately 0.02–0.03% of the earth's crust. Pure strontium is a pale yellow solid, but because of its highly reactive nature, strontium is generally found as molecular compounds with other elements. Commercially important strontium minerals include celestite ($SrSO_4$) and strontianite ($SrCO_3$). For economic reasons, strontium has not been mined in the United States since 1959, and strontium minerals are generally imported for commercial use. Strontium is used in the manufacture of ceramics and glass products, primarily in the faceplate glass of televisions and other cathode-ray-tube devices, where it serves to block x-ray emissions. Other uses of strontium compounds include pyrotechnics, paint pigments, fluorescent lights, medicines, and the production of zinc and aluminum products. Most stable strontium minerals and compounds do not require special disposal or handling requirements. However, depending on the associated cation, some chemical forms are classified as hazardous material, for example, the carcinogen strontium chromate.

Strontium is widely distributed in the earth's crust and oceans. It is released into the atmosphere as a result of natural processes such as entrainment of dust particles, resuspension of soil by wind, and sea spray. Strontium is released into surface water and groundwater from the natural weathering of rocks and soils. Human activities, including milling and processing of strontium compounds, burning of coal, land application of phosphate fertilizers, and use of pyrotechnic devices, release strontium into the atmosphere. Discharges of industrial waste water and runoff from land treated with phosphate fertilizers are human-related processes that release strontium into streams and aquifers.

The general population is exposed to stable strontium primarily by ingestion of food and water, and to a lesser degree, by inhalation. The strontium content in air averages 20 ng/m^3, with higher concentrations resulting from stack emissions from coal-burning plants. Strontium is present in nearly all fresh waters in amounts generally ranging between 0.5 and 1.5 mg/L, with higher levels occuring where there are

celestite-rich limestone deposits. The average concentration of stable strontium in soil is approximately 240 mg Sr/kg, but agricultural soils may be treated with phosphate fertilizer or limestone, which contain ~610 mg Sr/kg. Because strontium is chemically similar to calcium, it is taken up from the soil by fruits and vegetables. The average concentration of strontium in fruit produce ranged from 0.0416 to 2.232 µg/L. The total estimated daily exposure to stable strontium is approximately 3.3 mg/day: 400 ng/day from inhalation, 2 mg/day from drinking water, and 1.3 mg/day from the diet (see Chapter 6). Assuming a reference body weight of 70 kg, the typical daily strontium exposure is 46 µg/kg body weight. The strontium content of the human body is approximately 4.6 ppm by weight, 99% of which is localized in bones and teeth. Blood concentrations of strontium are in the range of 20–31 µg/L.

Radioactive Strontium.

The radioactive isotopes of strontium do not occur naturally but are produced as a by-product of nuclear fission of ^{235}U, ^{238}U, or ^{239}Pu. The most significant isotopes are ^{90}Sr (half-life 26 years) and ^{89}Sr (half-life 51 days), which decay by the emission of beta particles with energies of 0.546 and 1.495 MeV, respectively. ^{90}Sr is currently found in spent fuel rods in nuclear reactors and is considered a waste product. Other radioactive strontium isotopes have been employed for medical uses: ^{89}Sr (as Metastron™) as a cancer therapeutic for the relief of bone pain and ^{85}Sr (half-life 65 days; beta energy 1.065 MeV) in the radiologic imaging of bone. ^{85}Sr also has minor commercial applications in thermoelectric power generation, as a beta particle standard source, and in instruments that measure the thickness and density of materials. Disposal and handling of radioactive strontium isotopes are regulated by the Nuclear Regulatory Commission.

During the period 1945–1980, radioactive strontium was released into the atmosphere and widely distributed as a result of aboveground detonations of nuclear weapons. However, atmospheric deposition of ^{90}Sr has steadily decreased from a high in 1963 of approximately 3.0 MCi (1.10×10^8 Gbq) to <3,000 Ci in 1990, indicating a decline in fallout globally. Occasional regional contamination from radioactive strontium has occurred during large-scale nuclear power plant accidents such as the Chernobyl disaster in the Ukraine. In the United States, scheduled atmospheric releases from all nuclear power plants totaled 75.4 mCi (2.76 Gbq) of radioactive strontium in 1993 (Table 6-1). Other minor releases have involved accidents with rockets or satellites and routine releases from Department of Energy (DOE) nuclear fuel reprocessing plants. Radioactive strontium in the atmosphere is deposited on soil and in water as a result of rainfall. Nearly all soils in the United States contain ^{90}Sr, as a result of previous aboveground nuclear weapons testing. In the former Soviet Union, large scale regional contamination occurred between 1949

and 1956 from accidental and planned releases of radioactive liquid into the Techa River from a plutonium production complex. ^{90}Sr contributed about 12% or 0.23 MCi of the total released. The health of the population that used the Techa River as their main water supply has been monitored since that population received the highest known chronic oral exposure to radioactive strontium (and other radionuclides). At nuclear power plants and DOE sites in the United States, there have been intentional and unintentional releases of radioactive strontium directly into streams; in some cases, soils in the vicinity have been contaminated by leakage from storage basins and holding tanks. Releases of radioactive strontium into surface waters from nuclear power reactors in 1993 totaled 547.6 mCi (20.31 GBq). Radioactive strontium in soil bioaccumulates in food crops and livestock.

The general population is exposed to radioactive strontium from the ingestion of contaminated water and food; inhalation exposure is negligible. The average concentration of ^{90}Sr in drinking water in 1994 was estimated as 0.1 pCi/L. Fresh vegetables contribute more than one third of the yearly dietary intake of ^{90}Sr, followed by grains and dairy products. The concentration of ^{90}Sr in pasturized milk ranged between 0.23 and 2.12 pCi/L and averaged 0.6 pCi/L in 1997. Intake levels of ^{90}Sr in food have declined from a peak level of 30 pCi/day (1.1 Bq/day) in 1965 to <5 pCi/day (0.2 Bq/day) in 1989. Current total daily exposure levels to radioactive strontium are estimated to be approximately 5.2 pCi/day (0.16 Bq/day): 5 pCi/day from food and 0.2 pCi/day from drinking water. Assuming a 70-kg reference body weight, the general population exposure to radioactive strontium is 0.074 pCi/kg/day. The distribution of radioactive strontium in the human body is the same as for stable strontium; the major fraction is contained in the skeleton and teeth.

2.2 SUMMARY OF HEALTH EFFECTS

Stable Strontium.

As a ubiquitous nonessential trace element with chemical similarities to calcium, strontium appears to have low toxicity. *In vitro* studies demonstrate that stable strontium can substitute for calcium in biological processes, resulting in subtle changes, but significant effects *in vivo* are only observed at high dose levels. Abnormal skeletal development is the most significant effect of excess stable strontium. The data for adverse health effects of stable strontium in humans are sparse. One case report described an individual who had an anaphylactic reaction following inhalation of smoke containing strontium (and other materials) from a roadside flare (see Section 3.2.1 Respiratory, Cardiovascular, and Immunological Effects). In this study, the subject had a medical history of immunological sensitivity that may have

contributed to the outcome. One epidemiological study determined that the incidence of rickets in children living in a region of Turkey was related to the ingestion of foods grown in cropsoil with high levels of strontium (see Section 3.2.2, Musculoskeletal Effects). In a few incidents, strontium in dialysis water contributed significantly to osteomalacia in hemodialysis patients (see Section 3.2.5, Musculoskeletal Effects). Other studies reported benign effects of stable strontium. An epidemiological study found no positive association between strontium ingestion and certain kinds of heart disease (see Section 3.2.2, Cardiovascular Effects). Strontium chloride had no adverse effect on the function of stored human sperm in *in vitro* fertility assays (see Section 3.2.5). Numerous oral studies in animals demonstrated adverse effects of excess stable strontium on skeletal development (Section 3.2.2, Musculoskeletal Effects). In addition, excess strontium ingestion affected gastrointestinal and renal processes related to calcium absorption. One animal study found that high oral doses of strontium were clastogenic to rats, but all other genotoxicity studies were negative. One strontium compound, strontium chromate, is a genotoxic human carcinogen by the inhalation route, but the hazard is caused by hexavalent chromium.

Musculoskeletal Effects. Although strontium, as a molecular surrogate for calcium, can be distributed throughout the body, its main target organ is the skeleton. Excess strontium ingestion has been implicated as a contributing factor to the high prevalence in rickets among children living in the Ulaş Health Region of Sivas, Turkey. Other factors in this study included a probable deficiency in vitamin D, because of the lack of sunshine, and a deficiency in calcium in the diet after weaning. The potential skeletal toxicity of excess strontium in humans is supported by several reports indicating that hemodialysis patients have impaired handling of strontium and that strontium in dialysis water is a significant contributor to dialysis-associated osteomalacia.

Skeletal effects of stable strontium (chloride or carbonate) in animals have been analyzed in one acute-duration oral study and several intermediate-duration oral studies. Young animals were more sensitive to the effect of excess strontium than older animals, possibly because the absorption and retention of strontium were higher in the young. In addition, inadequate calcium and vitamin D in the diet increased the severity of skeletal effects. Excess strontium caused a reduction in bone mineralization (ash weight), and an alteration in the chemical composition of organic bone matrix. In addition, the hypertrophic zones of the epiphyseal growth plates of long bones became abnormally deep and wide, as calcification failed to occur. Severe weakening of the bones resulted in rickets, in which the skeleton could not support the body adequately; deformity of the head of the femur may have contributed to paralysis of the hind limbs in some cases. These effects occurred at relatively high doses. The chemical form of strontium may

influence toxicity by affecting gastrointestinal absorption. One intermediate oral animal study that tested strontium phosphate reported a much higher no-effect level than studies that tested strontium chloride or carbonate. Cation effects on strontium toxicity have not been studied systematically.

Evidence from the few human studies and numerous animal toxicity studies suggest that healthy adults living near hazardous waste sites are unlikely to be exposed to levels of stable strontium sufficiently high to cause adverse skeletal effects. Children living in areas where the soil and drinking water contain relatively high amounts of strontium may be vulnerable to skeletal effects if their nutritional status is poor and if the diet is restricted to foods grown locally. These conditions are not likely to be common in the United States, since the food supply generally comes from a wide geographic area. In addition, pasteurized milk sold in the United States is fortified with vitamin D, so that individuals who drink milk are protected against the adverse skeletal effects of excess strontium.

Radioactive Strontium.

The basis of the adverse effects of ionizing radiation on human or animal tissue is the direct interaction of free radicals with cellular macromolecules, including DNA (see Appendix D Section D.4). Low-level exposures are not necessarily harmful, as shown by the lack of discernable adverse effect in the general population from chronic low-level exposure to ^{90}Sr in fallout during the period of aboveground weapons testing. Exposures to radioactive strontium become harmful when the amount of radiation damage exceeds the capacity of natural cellular repair mechanisms. External exposure to radioactive strontium resulted in dermal and ocular effects in humans and animals. Since absorbed radiostrontium is preferentially retained in bone, and therefore has a long biological half-life, all internal exposures, of whatever duration, will lead to chronic internal exposure to ionizing radiation. Consequently, the most significant effects of exposure to absorbed radioactive strontium are necrosis and cancers of bone and tissues adjacent to bone. High level acute exposures can lead to acute radiation sickness resulting from destruction of the hemopoietic bone marrow. Dystrophic or osteolytic lesions have been described in humans and animals following intermediate or chronic exposures. At lower levels of exposure, chronic suppression of immune function has been observed in humans and animals. In animal studies, inhalation of insoluble particles of radioactive strontium led to retention in the lung and resulted in pulmonary necrosis and cancer. The young are more susceptible to adverse effects of absorbed radioactive strontium because of their higher rates of gastrointestinal absorption and of strontium retention in the immature skeleton. High prenatal exposure levels may cause major developmental anomalies in the skeleton and adjacent areas if critical tissues are destroyed. In addition, since children have a higher proportion of

mitotic cells than adults, they are susceptible to higher rates of cancer because genetic lesions become fixed mutations when mitosis occurs before genetic damage is repaired. Persons with Paget's disease (osteitis deformans) may be vulnerable to radioactive strontium because of their higher than normal rates of retention in focal sites of bone deposition. The following paragraphs discuss significant effects of exposure to radioactive strontium: cancer, hematological, immunological and lymphoreticular, musculoskeletal, respiratory, cardiovascular, gastrointestinal, developmental, reproductive, dermal, ocular, and neurological effects. In addition to these, hepatic and renal effects were observed in animals following inhalation or oral exposure, but the significance for human exposure is unclear.

Cancer. Radioactive strontium, like other radionuclides, is a genotoxic carcinogen. Consumption of radioactive strontium (and other radionuclides) in food and water during the period of 1949–1956 significantly increased the incidence of leukemia in the Techa River population. No increase in cancer was observed in the offspring of radiation-exposed individuals in this region. No studies were located regarding an increase in cancer in humans following exposure to radioactive strontium by the inhalation or dermal routes. Numerous studies on animals demonstrated carcinogenic effects of inhalation, oral, and external exposure to radioactive strontium. Cancer was the most common cause of late deaths in animal studies, but the type and location of tumors varied with the route of administration. In dogs and rats exposed to soluble ^{90}Sr by inhalation, osteosarcoma was the most common type. Many early tumors in dogs were hemangiosarcomas, although carcinomas in soft tissues adjacent to the skull and leukemia from irradiation of the bone marrow were also detected. In dogs exposed to ^{90}Sr fused-clay particles, pulmonary hemangiosarcoma was the most common tumor, with the heart being the next most frequent site. Various carcinomas of the respiratory tract were also detected. In animals exposed to ^{90}Sr by the oral route, osteosarcoma and myeloid leukemia were most common, followed by oral, nasal, or periodontal carcinoma. In general, in the oral exposure studies, osteosarcoma occurred in the higher dose animals. Young animals were more sensitive to the carcinogenic effect of radioactive strontium. In the a multigenerational swine study, doses that were not carcinogenic in the females exposed as adults, induced osteosarcomas in the F1 or F2 generations exposed from conception. External exposure to ^{90}Sr (solid source) induced skin cancers (squamous cell carcinoma, basal cell carcinoma, fibrosarcoma) in mice, but there appeared to be variations in strain susceptibility. The dermis was more sensitive than the epidermis to the carcinogenic effects of ionizing radiation. In one mouse study, osteosarcomas developed following external exposure to ^{90}Sr. Numerous studies in several species reported the induction of malignant tumors in response to injection of radioactive strontium. In general, osteosarcomas and bone hemangiosarcomas developed at higher dose levels, and lymphomas and leukemias developed at lower levels. Carcinomas of soft tissues adjacent to bone also developed. The offspring of pregnant rats that were injected late in

gestation had an increased incidence of pituitary adenoma and meningeal sarcoma or tubular adenoma of the ovaries.

On the basis of data from the Techa River populations and from experimental animal studies, exposure to radioactive strontium by any route could be expected to cause cancer. However, the National Council on Radiation Protection and Measurements concluded that uncertainties remain regarding extrapolation from the high doses of ^{90}Sr known to cause cancer in animals to the lower doses that might increase the incidence of leukemia in humans. The Council suggested that more basic knowledge on the mechanism of cancer induction by ionizing radiation would be required to understand the risk of internal exposure to ^{90}Sr. The EPA has determined that radioactive strontium is a known human carcinogen. The International Agency for Research on Cancer (IARC) has determined that internally deposited radionuclides, such as radioactive strontium, are carcinogenic to humans (Group 1).

Hematological Effects. In the Techa River populations that accidently consumed radiostrontium and radiocesium between 1949 and 1956 (and received simultaneous exposures to external gamma irradiation), leukopenia, thrombocytopenia, and granulocytopenia developed in >3% of exposed individuals. No human studies were located regarding hematological effects in humans following exposure to radioactive strontium by the inhalation or dermal routes. Animal studies in several species (monkey, rat, rabbit, dog, cow, and miniature swine) demonstrated that hematological effects are the most serious immediate consequences of exposure to high levels of radioactive strontium by either the inhalation or oral route. When absorbed radioactive strontium incorporates into bone, irradiation of the bone marrow results in hypoplasia of the hemopoietic tissue and pancytopenia, with the severity depending on the dose. The most severely afflicted animals, whose bone marrow becomes aplastic, die from acute radiation syndrome within weeks of exposure. A terminal symptom in these animals, hemorrhage, appears to be related to the drastic depression in platelet counts. A severe reduction in neutrophil counts was found to be the most reliable predictor of death in dogs exposed to $^{90}SrCl_2$ by inhalation. In several species, neutrophil and lymphocyte counts were reported to remain significantly lower than normal for years following exposure. This could be expected to adversely affect the ability to resist infectious disease.

These findings are supported by several clinical studies in which ^{89}Sr, one of the shorter-lived radioactive isotopes of strontium, has been used in cancer therapy for the relief of pain from tumors that have metastasized to the bone marrow. Aside from the destruction of tumors, significant reductions in platelet and/or white blood cell counts persisted for up to 12 months after patients were injected with a single

therapeutic dose. Similar effects have been observed in animals. Hypoplasia of the bone marrow has been observed in mice injected with ^{90}Sr or ^{89}Sr, the latter of which has been used intentionally to create mice with aplastic bone marrow. CBA/J mice injected with fixed doses of ^{89}Sr that differed in the specific activity of the preparation showed quantitative differences in the degree of bone marrow suppression. Acute hematological symptoms (depression of hemopoiesis leading to anemia or hemorrhage, transient neutropenia, and chronic leukopenia, depending on the dose) were observed in beagles beginning several weeks after injection of ^{90}Sr.

Immunological and Lymphoreticular Effects. In the Techa River populations that accidently consumed radiostrontium between 1949 and 1956 (and received simultaneous exposures to other radionuclides), long-term immunological disorders were reported. Evidence of immunosuppression included decreases in T lymphocytes and large granulocytic lymphocytes that were most severe in individuals exposed *in utero* or during the first 2 years post-gestation. The weakened immune system was suggested to contribute to the development of radiation-induced cancers, since individuals with tumors had higher incidences of infectious disease. No studies were located regarding immunological or lymphoreticular effects in humans following exposure to radioactive strontium by the inhalation or dermal routes.

In animals, profound effects on the immune and lymphoreticular systems were sequelae of exposure to radioactive strontium by the inhalation or oral routes. Lymphopenia and immunosuppression (reduced antibody titers) were noted in beagles exposed to soluble aerosols of $^{90}SrCl_2$. In beagles exposed by inhalation to relatively insoluble ^{90}Sr fused-clay particles, thoracic lymph nodes were destroyed by radioactive particles that were transported out of the lung and lymphocyte counts were suppressed for >2 years. Chronic ingestion of radioactive strontium suppressed immune function in pigs and induced myeloid metaplasia in both pigs and dogs. Immunological or lymphoreticular effects in humans could be a concern in some exposure scenarios.

Evidence from injection studies in animals corroborates the sensitivity of the immune system to radioactive strontium. In mice that have been injected with ^{89}Sr or ^{90}Sr to deplete bone marrow, natural killer cells are preferentially eliminated. The loss of this cell population results in a reduced ability to defend against lymphoid tumors. In similar injection studies, adverse effects have were also observed in the spleen and thymus.

Musculoskeletal Effects. Dystrophic lesions of the skeleton, primarily affecting articular and periarticular tissues, were reported in the Techa River populations that were chronically exposed to radiostrontium in contaminated food and water. The incidence of these lesions was related to the radiation dose to the bone.

In several species, ingested radioactive strontium incorporated into bone caused severe radiation damage to teeth, bone, and bone-associated tissues. Effects were most severe in young animals because their relative absorption and skeletal incorporation of strontium are higher than in adults. In developing animals, radiation damaged the vasculature of the long bones, changing the status of metaphyseal cartilage so that it ceased undergoing transformation into bone and resumed its proliferative status. Bone structure was weakened, sometimes to the extent of fracturing, by the incorporation of localized patches of cartilage and fibrous marrow into what should have been dense cortical bone. In adult animals, effects included a reduction in osteocyte numbers, mild trabecular osteoporosis, endosteal and periosteal cortical sclerosis and thickening, mottling or focal osteolytic lesions, and osteodystrophy. Dental effects in immature teeth included disordered tooth structure and increased cell death of differentiating odontoblasts and pulp cells. Mature teeth were not affected as severely.

Respiratory Effects. No studies were located regarding respiratory effects in humans following exposure to radioactive strontium by any route. Acute inhalation studies in dogs reported respiratory effects following exposure to particulate radioactive strontium. Acute exposure to relatively high levels of ^{90}Sr fused-clay particles, which were retained in the lung for long periods, resulted in radiation pneumonitis and/or pulmonary fibrosis and primary lung cancers. These effects could occur in humans exposed to particulate, insoluble radioactive strontium dust.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans following exposure to radioactive strontium. Following acute inhalation of ^{90}Sr fused-clay particles, considerable radiation damage to the vasculature of the lungs, and to the myocardium of the right atrium occurred in beagles because of the beta emissions released from particles embedded in the lung and lung-associated lymph nodes. Inhalation of soluble $^{90}SrCl_2$ did not induce these effects, since it was readily absorbed by the lungs and distributed throughout the body. Hemangiosarcomas resulting from ^{90}Sr fused-clay particles are discussed in the Cancer section above. Hemorrhaging, which occurred at high exposure levels in the $^{90}SrCl_2$ inhalation study and the chronic oral study in beagles, was a consequence of thrombocytopenia (see Hematological Effects section above). External exposure to radiation from ^{90}Sr solid sources apposed to the skin was reported to increase vascular permeability to plasma protein in

guinea pigs. These inhalation and dermal effects could occur in humans given a sufficiently large exposure. However, reported releases of radioactive strontium from nuclear power plants appear to be generally lower than the concentrations used in these experiments (see Table 6-1).

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans following exposure to radioactive strontium isotopes. In dogs dying soon after exposure to high levels of soluble $^{90}SrCl_2$ by inhalation, anorexia and bloody diarrhea were some of the manifestations of acute radiation syndrome. In the same study, several dogs surviving into old age developed a malabsorption syndrome characterized by chronic diarrhea, anorexia, and chronic degenerative and inflammatory lesions of the small intestine. These effects are potentially relevant to human health.

Developmental Effects. Slight increases in child mortality from chromosomal defects and from congenital anomalies of the nervous system, circulatory system, and other unspecified anomalies were reported in the progeny of the radiation-exposed population of the Techa River region. However, the contribution of radioactive strontium to this effect is uncertain. No studies were located regarding developmental effects in humans following exposure to radioactive strontium by the inhalation or dermal routes.

Studies in animals indicated that lifetime oral exposure to radioactive strontium from the time of conception had no immediate teratogenic effects, but there were dose-related effects on the lifespan of the F1 generation from bone-related cancer or other causes. Administration of radioactive strontium into pregnant animals by injection resulted in substantially more severe developmental effects, probably because the internal doses were relatively high. In these studies, increased mortality, skeletal anomalies, meningeal and pituitary tumors, partial atelectasis of the lungs, hyperplasia of lymph nodes and spleen, and deficient hematopoiesis were observed in offspring exposed during gestation following a single maternal injection. Exposure to high levels of radioactive strontium during the latter stage of gestation, when bone mineralization is increasing, would be likely to increase the lifetime risk of radiation-induced cancer effects in humans. However, reported releases of radioactive strontium by nuclear power facilities appear to be much lower than the dose levels used in animal experiments (see Table 6-1).

Reproductive Effects. No significant effect on reproduction (birth rate, fertility, incidence of spontaneous abortion) was found in the Techa River populations following accidental consumption of radiostrontium (and other radionuclides) between 1949 and 1956. Parental gonadal radiation doses were

primarily derived from external gamma radiation. No studies were located that addressed reproductive effects *in vivo* in humans following exposure to radioactive strontium by the inhalation or dermal routes.

Studies in several animal species suggest that the occurrence of reproductive effects following maternal exposure to radioactive strontium is dose-dependent. Most oral exposure studies found no adverse effect on reproduction, although increased fetal mortality was observed in one acute study and postnatal survival was decreased in several long-term studies. Numerous animal studies demonstrated adverse reproductive effects of injected radioactive strontium. Increased fetal mortality was observed when either the dams or sires were injected prior to mating. Dose-related adverse effects on gonadal development, more severe in females than in males, were observed in mice exposed *in utero* by maternal injection. Effects included suppression of spermatocyte maturation in male offspring and a reduction in the number of differentiating oocytes in the ovary of female offspring. The reproductive capacity (number of fertile females, number of litters, number of young per litter) of females treated *in utero* was significantly reduced at the higher doses. Ovarian cellularity of newborn mice was also affected by exposure to contaminated milk of injected dams. These studies suggest that reproductive capacity, particularly in females, may be adversely affected by gestational or lactational exposure to high levels of radioactive strontium. However, the exposure levels used in these studies are high compared to reported releases of ^{90}Sr from nuclear power facilities (see Table 6-1).

Dermal Effects. Dermal toxicity of radioactive strontium has been demonstrated in human and animal external exposure studies in which solid sources of ^{90}Sr (with daughter radionuclide ^{90}Y) were positioned on or close to the skin. A single human study reported late-developing side effects following the therapeutic/cosmetic irradiation of facial hemangiomas in children and adults treated repeatedly over 6–16 months. One third of the patients developed effects 8–10 years later that included achromia, excess pigmentation, slight atrophy, and telangiectasis.

Acute dermal reactions to ^{90}Sr have been described for mice, guinea pigs, and pigs. Below a certain field size, skin reactions depended upon the size of the area exposed, since recovery required the migration of healthy cells into the damaged area. Thus, the smallest fields require the highest exposure levels to elicit severe effects. The typical acute skin reaction, as described for mice, includes increasing erythema and pigmentation changes following an asymptomatic period of days, then dry desquamation and moist desquamation. These changes involve destruction of the basal epithelial cells, and long-term responses may involve epithelial and dermal hyperplasia, driven by enhanced expression of transforming growth factor beta-1 (TGF-β-1) in the skin. It is thought that continued expression of TGF-β-1 in the skin may

account for the chronic fibrosis that develops about 3 months after exposure in mice. In pigs, dermal atrophy was reported to occur in irradiated skin several years after an acute exposure. Dermal effects would be likely to occur in humans following a sufficiently severe dermal or external exposure to radioactive strontium. It is not certain that populations living near hazardous facilities would be exposed to such high levels except under unusual circumstances.

Ocular Effects. Several clinical studies reported complications resulting from the use of solid ^{90}Sr sources in the postsurgical irradiation of pterygia sites to prevent neovascularization. Adverse effects included keratitis of the cornea, telangiectasis or scarring of the conjunctiva, scarring of the cornea, iritis, conjunctivitis, mild irritation, and in one diabetic patient, scleral thinning.

Beagles exposed to ^{90}Sr from mid-gestation and then orally for more than a year developed benign melanoma of the eye. In other beagles that developed a myeloproliferative disorder, myeloid infiltration affected the eye, as well as other parts of the body. Ocular lesions (degeneration, hemorrhage, or hemosiderosis of the retina; fibrosis or vascularization of the cornea, hyperpigmentation, or inflammation of the cornea or iris; vacuolization of the lens) developed in beagles that had been injected with ^{90}Sr. The evidence is insufficient to predict ocular effects in humans following inhalation or oral exposure to radioactive strontium.

Neurological Effects. Neurological effects (weakness, apathy, and fatigue) were reported in the Techa River populations that were chronically exposed to radiation between 1949 and 1956. It is probable that exposure to external gamma radiation contributed to these effects and the role of radiostrontium is uncertain. No studies were located regarding neurological effects in humans following exposure to radioactive strontium by the inhalation or dermal routes. A single instance of epilepsy was noted among beagles that were exposed by inhalation to the highest concentration of $^{90}SrCl_2$, but this was thought to be unrelated to treatment.

2.3 MINIMAL RISK LEVELS

Inhalation MRLs

Stable Strontium. Data on the toxicity of inhaled stable strontium are limited to a case report of a woman exposed to an undetermined concentration of strontium from an ignited flare (Federman and Sachter 1997).

Radioactive Strontium. The main sources on the toxicity of inhaled radioactive strontium are two acute-duration beagle studies that have not yet been completed. The available interim reports suggest that acute inhalation exposure to ^{90}Sr results in severe chronic hematological and immunological effects in beagles. Inhalation of ^{90}Sr fused-clay particles leading to initial lung burdens of 5 µCi ^{90}Sr/kg (185 kBq/kg) resulted in chronic significant depression of lymphocyte counts and suppression of immune function (Jones et al. 1976). Inhalation of soluble $^{90}SrCl_2$ resulted in chronic thrombocytopenia and neutropenia that persisted for 1,000 days in dogs at all exposure levels (long-term retained burdens >1 µCi ^{90}Sr/kg (0.04 MBq/kg) (Gillett et al. 1987a). Since these effects are serious lowest-observed-adverse-effect levels (LOAELs), and relevant to known human responses to ionizing radiation, the data are not suitable for deriving inhalation MRLs for radioactive strontium.

Oral MRLs

Stable Strontium.

- An MRL of 2.0 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to stable strontium and its compounds.

The most consistent effects of oral exposure to excess stable strontium are rickets (impaired cartilage calcification) and osteomalacia (impaired bone mineralization), especially in the young. One Turkish epidemiological study provided indirect evidence that excess oral exposure to strontium (in the presence of other predisposing factors) may contribute to the development of rickets in children (Ögzur et al. 1996). In young rodents, typical effects of excess strontium included an abnormal widening of the cartilaginous epiphyseal plates of the long bones, a lack of bone calcification, and abnormal deposition of unmineralized bone matrix or osteoid (Johnson et al. 1968; Kshirsagar 1976; Marie and Hott 1986; Morohashi et al. 1994; Neufeld and Boskey 1994; Storey 1962). The skeletal effects of strontium are known to be related to its chemical similarity to calcium, and to its suppression of vitamin D metabolism and intestinal calcium absorption (Armbrecht et al. 1998). Effects are more severe in young rats than in adults, because the rate of skeletal incorporation of strontium is higher in young animals (see Section 3.4.2.2).

A LOAEL of 550 mg strontium/kg/day is identified for bone mineralization abnormalities in weanling rats that were exposed to dietary strontium carbonate for 20 days (Storey 1961). The epiphyseal plates of long bones were irregular and abnormally thick. Furthermore, areas of uncalcified bone matrix were deposited in the distal ends of the metaphyseal trabeculae and proximal end of the diaphyses.

Irregularities in the organization of the cells of the hypertrophic zone, in the pattern of calcification, and in the deposition of osteoid were more conspicuous with increasing dose. In tibias, the dry weight, ash weight, ash percentage, and calcium in ash were significantly reduced with increased strontium intake. No effects on bone mineralization occurred in weanling rats ingesting 140 mg strontium/kg/day. In adult rats examined in this study, the effects of strontium ingestion were less severe in that higher doses were required to produce the same effect. The no-effect level in adults was 690 mg strontium/kg/day, which was higher than the LOAEL for weanlings. In adults, changes in tibial histology, such as abnormal thickening of the epiphyseal cartilages and abnormally widened metaphyseal osteoid seams, were noted at or above 1,370 mg strontium/kg/day. At 2,750 mg strontium/kg/day, osteoid tissue was deposited near vascular canals, and the areas of bone resorption were reduced. In adult rat tibias, the dry weight, ash weight, ash percentage, and calcium in ash were only significantly affected at the highest dose. This study demonstrates the difference in sensitivity to strontium between young and old animals, which is caused by the higher rate of strontium incorporation into the developing skeleton in young animals.

The critical dose levels identified in the Storey (1961) study are supported by other studies in rodents. Similar LOAELs (500–565 mg strontium/kg/day) for abnormal bone mineralization are identified in several studies on weanling rats (Johnson et al. 1968; Morohashi et al. 1994; Neufeld and Boskey 1994). Slight skeletal effects were noted in mice at 350 mg/kg/day (Marie and Hott 1986). In addition, similar no-observed-adverse-effect levels (NOAELs) in the range of 110–168 mg strontium/kg/day for skeletal effects are identified from studies in weanling rats (Grynpas et al. 1996; Kroes et al. 1977; Morohashi et al. 1994). Several of these studies tested a single dose level, and therefore do not provide a sufficient basis for deriving an MRL (Grynpas et al. 1996; Johnson et al. 1968; Marie and Hott 1986; Neufeld and Boskey 1994). The study of Kroes et al. (1977) did not include an adverse dose level, whereas the no-effect level in the study of Morohashi et al. (1994) is lower than the NOAEL for weanlings in Storey (1961). Therefore, the NOAEL of 140 mg strontium/kg/day for skeletal effects in weanling rats would appear to be the most appropriate basis for calculating an intermediate MRL. Applying to the 140 mg strontium/kg/day NOAEL an uncertainty factor of 30 (10 for extrapolation from animal to human and 3 for human variability) and a modifying factor of 3 (for short study duration and limited end point examination), the MRL is calculated to be 2.0 mg strontium/kg/day. This is approximately 40 times higher than the total estimated daily exposure to stable strontium of 47 µg/kg/day (see Section 6.5). The MRL represents an estimate of daily human exposure that is likely to be without an appreciable risk of adverse health effects. Since the MRL is based on effects in young rats, it is considered to be protective of children, who are similar with respect to immaturity of the skeleton and high intestinal rates of strontium absorption. The MRL is not intended to support clean-up or other regulatory action, but to

serve as a guideline for health assessors to consider when making recommendations to protect populations living in the vicinity of a hazardous waste site or substance emission.

MRLs were not derived for acute- or chronic-duration oral exposures to stable strontium. The relevant acute data are limited to two lethality studies in mice and two toxicity studies in rats. One of the rat studies used a high dose causing serious body weight effects (Kshirsagar 1976). In the other study (Kroes et al. 1977), the high dose was a NOAEL for skeletal effects (110 mg strontium/kg/day) that is lower than the NOAEL identified in Storey (1961) as the basis for the intermediate MRL (140 mg/kg/day). Therefore, the dose levels tested in the available acute oral studies do not cover the range likely to provide an acute oral MRL. There are no chronic-duration oral studies upon which to base a chronic oral MRL for stable strontium.

Radioactive Strontium. No MRLs were derived for oral exposure to radioactive strontium, although the database includes chronic-duration human studies and acute-, intermediate-, and chronic-duration animal studies in several species. Although strontium dosimetry information is available for the populations affected by contamination of the Techa River, the exposures included simultaneous external gamma radiation from ^{137}Cs, ^{106}Ru, and ^{95}Z and internal radiation from ^{137}Cs, in addition to ^{89}Sr and ^{90}Sr (Kossenko et al. 1994). The combined exposure studies are not suitable for the derivation of MRLs. Most of the animal studies reported serious hematological effects at all dose-levels. The miniature swine chronic-exposure study reported no adverse effects at the two lowest doses, but dosages were reported on a per animal basis (Clarke et al. 1972). Growth-curve data for the Pitman-Moore strain of miniature swine were not available, so the doses cannot currently be expressed in terms of kilograms of body weight, which is necessary for deriving an MRL.